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UNGAR, SUSAN NMN

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Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No. 10/054,935	Applicant(s) Sun et al
Examiner Ungar	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

1)  Responsive to communication(s) filed on Apr 23, 2003

2a)  This action is FINAL. 2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

### Disposition of Claims

4)  Claim(s) 1-27 is/are pending in the application.

4a) Of the above, claim(s) 9-27 is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 1-8 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are a)  accepted or b)  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)  The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some\* c)  None of:

1.  Certified copies of the priority documents have been received.

2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)  The translation of the foreign language provisional application has been received.

15)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

1)  Notice of References Cited (PTO-892)

4)  Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_

2)  Notice of Draftsperson's Patent Drawing Review (PTO-948)

5)  Notice of Informal Patent Application (PTO-152)

3)  Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_

6)  Other: \_\_\_\_\_

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1. The Election filed April 23, 2003 (Paper No. 4) in response to the Office Action of March 25, 2003 (Paper No. 3) is acknowledged and has been entered. Claims 1-27 are pending in the application and Claims 9-27 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-8 are currently under prosecution
2. Applicant's election with traverse of Group I, claims 1-8 in Paper No 4 is acknowledged. The traversal is on the ground(s) that search of all of the inventions would not be undue because the inventions comprise overlapping subject matter. This is not found persuasive because the literature search, particularly relevant in this art, is not coextensive and different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

***Specification***

3. The disclosure is objected to because of the following informalities:
  - (1) page 6 ends with an incomplete sentence which is not completed on page 7;
  - (2) the specification has spelling errors, for example, page 31, line 25 wherein the specification recites the term "abreast". Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where other spelling errors may be found. Appropriate correction is required.

***Claim Objections***

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4. Claim 2 is objected to because the claim is incomplete. As currently constituted it reads in-part, "An isolated of claim 1". Appropriate correction is required.
5. Claim 7 is objected to because the claim is drawn to a polynucleotide that "is effective". The phrase "is effective" is indefinite when the claims fail to state the function which is to be achieved. See *In re Frederiksen & Nielsen*, 213 F 2d 547, 102 USPQ 35 (CCPA 1954).

***Claim Rejections - 35 USC § 101***

6. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

7. Claims 1-8 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility, a well established utility, a substantial utility.

The disclosed utilities for the claimed Urb-ctf polynucleotide (SEQ ID NO:1) or variants thereof encoding the Urb-ctf polypeptide (SEQ ID NO:2) or fragments thereof include their use as a marker to determine the presence of breast cancer in normal breast tissue for diagnostic and therapeutic applications, their use in transcriptional assays such as the yeast two-hybrid system (p. 4), the claimed polynucleotides can be used for screening a genomic library or the sequence can be used for searching nucleotide databases such as GenBank and Embl for matches,

(p.7) for homologs. Further the encoded polypeptide and fragments thereof can be used to produce antibodies, as competitors to DNA-binding, dimerization or transcriptional activities. The specification further teaches that the claimed polynucleotide encoding Urb-ctf and the encoded polypeptide are useful for diagnosing breast cancer, or determining susceptibility to it (p. 31, lines 24-26), they can be used to assess the effects of therapeutic and preventative interventions (p. 33, lines 9-25), they can be used to identify agents that modulate Urb-ctf (p. 34, lines 5-10), they can be used in detection arrays and for screening libraries(p. 39) or to make transgenic animals (p. 40), can be used in electronic databases (p. 44). However, neither the specification nor any art of record teaches what Urb-ctf is, what it does do, they do not teach a utility for any of the fragments or the variants claimed. Although the specification asserts that Urb-ctf is overexpressed in breast cancer the specification does not enlighten the artisan as to whether it is the polynucleotide and/or the polypeptide that is overexpressed. The specification does not enlighten the artisan as to why this conclusion was reached, does not enlighten the artisan as to the methods used to make the determination. Was the determination made based on Southern blot data, Northern blot analysis using physical samples from tumor and normal tissue, electronic Northern analysis using database comparison data, ELISA, RIA? Aside from the apparent hypothesis of an association of Urb-ctf to breast cancer, no relationship to any specific disease or involvement in the etiology of any specific disease has been established. The asserted utilities for Urb-ctf, such as its use in a two-hybrid system, screening of libraries, both physical and electronic for homologs, the use of the encoded

polypeptide for the production of antibodies, their use for identifying agents that modulate Urb-ctf, their use in detection arrays, the making of transgenic animals and their use in electronic databases apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to Urb-ctf. Additional uses for Urb-ctf polynucleotide, and polypeptide encoded thereby, include their use as a marker to determine the presence of breast cancer in normal breast tissue for diagnostic and therapeutic applications, for determining susceptibility to breast cancer, for assessing the effects of therapeutic and preventive interventions.

The breast cancer-related asserted utilities of Urb-ctf are based on the assertion that Urb-ctf has a normal functional role in most tissues since it can be detected in most tissues examined but either none or at very low levels in normal breast tissue, thus it can be involved with diseases associated with most normal tissues as well as diseases in normal breast tissue (p. 4, lines 7-10). However, as noted above, although the specification teaches that Urb-ctf is overexpressed in breast cancer the specification does not enlighten the artisan as to whether it is the polynucleotide and/or the polypeptide that is overexpressed. Since no data is presented and no teaching has been made as to how the association of the claimed polynucleotide/encoded polypeptide was determined, it will be assumed for examination purposes that it is the polynucleotide and not the polypeptide that is overexpressed in breast cancer tissue as compared with normal cancer tissue. Further, because no data is presented, it will be assumed for examination purposes that the expression of the polynucleotide was assessed in electronic libraries of the

tissues and that the libraries contain representative sequences of polynucleotides from those tissues. Given these basic assumptions, it cannot be determined from electronic libraries whether or not a given polynucleotide sequence is differentially expressed in one tissue compared to another because Thompson et al (Genome Research, 2002, 12:1517-1522) reveals a basic flaw in the use of electronic Northern database systems. For example, as drawn to electronic Northern data, Tables 2 and 3 (on pages 1518-1519) report the use of GAPD as a reference. It is noted that the use of GAPD as a reference for Northern Blot analysis is conventional because it is known that GAPD is expressed in every human cell that expresses mRNA. However, a review of Table 2 reveals that PSG1 was found in 13 different electronic libraries and that the number of these libraries in which both PSG1 and the GAPD are found is only 11. Further, a review of Table 2 reveals that PEDF was found in 27 different electronic libraries and that the number of these libraries in which both PEDF and GAPD are found is only 10. If these libraries were truly representative, GAPD would be included in the libraries. Given that these electronic libraries are from cDNA libraries that have been sequenced, it appears that not all of the cDNAs in the all of the source libraries have been sequenced or included in the electronic libraries and the electronic libraries are not representative of the mRNA population of the cell types from which the sequenced cDNAs were derived. In particular, Soares et al (PNAS, 1994, 91:9228-9232), teaches that the  $5 \times 10^6$  mRNA molecules of a typical somatic cell are distributed in three frequency classes that are presumably maintained in representative cDNA libraries. The classes at the two extremes, i.e. 10% and 45 % of the total, include members that

occur at vastly different relative frequencies. The class that represents 10% of the mRNA, most prevalent class, consists of about 10 mRNA species, each representing 5000 copies per cell, whereas the class of high complexity (that represents 45% of the mRNA) comprises 15,000 different species each represented by only 1-15 copies (p. 9228, col 1). It is unknown whether each of the electronic libraries used in the analysis of Thompson et al includes cDNA of each of the more than 15,000 species of mRNA expressed in typical somatic cells and if not, which of the mRNA species has not been included. This basic flaw of electronic cDNA databases is further exemplified, for example by, Yerushalmi et al (Gene, 2001, vol. 265, pp. 55-60) who teach that the gene for ERGL was indicated to be expressed exclusively in the prostate by electronic database searching, however, Northern blot hybridization indicated that the gene was also expressed in cardiac atrium, salivary gland, spleen and selective cells in the CNS. In contrast, Caillou et al (Journal of Clinical Endocrinology and Metabolism, 2001, Vol. 86, pp. 3351-3351) reports that Northern blot analysis of different human tissues demonstrated that the LNOX gene was expressed only in the thyroid gland, while blast analysis of expressed sequences indicated that the LNOX gene is expressed in non-thyroid tissues.

Given the above, the use of electronic Northern data to determine differential expression or expression in one tissue versus another tissue is clearly unpredictable. Given the teaching of Soares et al, Thompson et al, Yerushalmi et al, Caillou et al it is clear that it cannot be predicted that SEQ ID NO:1 is overexpressed in breast cancer because it cannot be determined from the information in the electronic databases if SEQ ID NO:1 is overexpressed in the cell from which the cDNAs were

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used to provide the sequence data for the library because it cannot be determined whether all of the copy numbers of SEQ ID NO:1 from that cell type and the control cell types are accurately represented.

Further, in terms of mRNA species in cells which form the basis for the sequenced cDNAs in electronic libraries, Sambrook (*A Laboratory Manual*, 2<sup>nd</sup> Ed., Sambrook et al, Eds, 1989, Cold Spring Harbor Laboratory Press) specifically teaches that a typical mammalian cell contains between 10,000 and 30,000 different mRNA sequences and that the proportional representation of each sequence depends on its rate of synthesis and half-life (p. 8.6). A review of electronic database libraries, reveals that many of these libraries contain 5,000-10,000 sequences. Clearly none of these come close to the number of transcripts found in a typical mammalian cell as disclosed by Sambrook et al, or of those found in a typical somatic cells as disclosed by Soares et al, above. Given the above, it is not clear how one could determine the relative abundance of any one gene product, in particular, it is not clear how one could determine whether a mRNA is overexpressed in breast cancer as compared to a normal control using electronic Northern analysis based on an electronic Northern library.

Northern electronic libraries cannot be used to determine the relative abundance of gene products because Sambrook, et al, *Supra*, clearly teaches that the method for determining the number of clones necessary to construct a complete cDNA library has been determined. Construction of a cDNA library from a human fibroblast cell that contains approximately 12,000 different mRNA species is exemplified. Low abundance mRNAs (less than 14 copies/per cell) constitute

approximately 30% of the mRNA and there are about 11,000 different mRNAs belonging to this class. The minimum number of cDNA clones required to obtain a complete representation of mRNAs of this class is therefore  $11,000/.30$  or 37,000. Of course because of sampling variation and/or preferential cloning of certain sequences, a much larger number of recombinants must be obtained to increase the chance that any given clone will be represented in the library. In order to achieve a 99% probability of obtaining an mRNA present in human fibroblasts at a frequency of 14 molecules/cell, the number of clones required is 170,000 (pgs 8.6-8.7). It is noted that Old and Primrose (*Principles of Gene Manipulation, An Introduction to Genetic Engineering*, 1989, Blackwell Scientific Publications, Osney Mead, Oxford) specifically teach for a reasonably complete cDNA library, typically  $10^6$ - $10^7$  are sufficient clones for most cell types (p. 122, last para). Given the above, again, assuming that the determination of SEQ ID NO:1's association with breast cancer is based on electronic northern data, although it is clear that the normal breast tissue databases do not include SEQ ID NO:1 or express SEQ ID NO:1 at low levels, the fact that they do not include SEQ ID NO:1 cannot be extrapolated to a hypothesis that the cells from which they are derived also do not express SEQ ID NO:1 for the reasons set forth above. Further, the corollary is true, that is, although SEQ ID NO:1 is overexpressed in tumor breast tissue, this fact cannot be extrapolated to a hypothesis that the cells from which it is derived also overexpress SEQ ID NO:1 for the reasons set forth above. All that the data shows is that in the Databases that are shown to express SEQ ID NO:1, that SEQ ID NO:1 can be found in that database. Although one can determine what the abundance of SEQ ID NO:1 is in that

database, one cannot determine what the abundance of SEQ ID NO:1 is in the cell from which it was derived as no nexus has been established between the % abundance in an electronic database and any living cell. Further, it cannot be determined, and given the teaching of the art it would not be expected, that all of the copies of SEQ ID NO:1 are represented in any of the databases, either normal or diseased that have been assayed since it is clear from Sambrook et al that even for human fibroblasts, it is necessary to have 170,000 clones to have a 99% probability of identifying a cDNA clone of an mRNA present in human fibroblasts. In the absence of a correlative nexus established between electronic databases and the *in vivo* cell environment, in the absence of objective evidence, for example clinical Northern Blot analysis, demonstrating that SEQ ID NO:1 is differentially expressed in breast cancer tissue as compared to normal controls, additional work must be done in order to determine a real-time use for the claimed sequence and to determine whether or not SEQ ID NO:1 is indeed differentially expressed in breast cancer as compared with normal controls, in order to establish that it can be used for diagnosis of breast cancer, in order to establish that it can be used for the treatment of breast cancer and to determine a real-world use for the claimed polynucleotide. Again, the claimed polynucleotide does not have substantial utility.

Further, even if it were to be established that Urb-ctf is differentially expressed in breast cancer patients compared to normal controls this does not establish that the encoded polypeptide is also differentially expressed. In particular, it is well known in the art that the regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen, M. Et al, 1995,

Pediatric Res., 37(6):681-686). Further, those of skill in the art, recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Thus, predictability of protein translation is not necessarily contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, one of skill in the art would not be able to predict if SEQ ID NO:2 could in fact translated into a polypeptide expression product, or that it is differentially expressed in breast cancer

patients compared to normal control. Thus, although the specification states that Urb-ctf is differentially expressed, additional work must be done in order to establish that Urb-ctf is in fact differentially expressed in breast cancer tissue compared to normal controls, in order to establish that it can be used for diagnosis of breast cancer, in order to establish that it can be used for the treatment of breast cancer and to determine a real-world use for the encoded polynucleotide. Thus, the claimed polynucleotide does not have substantial utility.

Further, evidence abounds in which protein levels do not correlate with, steady-state mRNA levels or alterations in mRNA levels. For instance, Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teach that high levels of the mRNA for TNF alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable. Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and the protein level, indicating that S100 protein is post-transcriptionally regulated. Eriksson et al (Diabetologia, 1992, vol. 35, pp. 143-147) teach that no correlation was observed between the level of mRNA transcript from the insulin-responsive glucose transporter gene and the protein encoded thereby. Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Powell et al (Pharmacogenetics, 1998, Vol. 8, pp. 411-421) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Carrere

et al (Gut, 1999, vol. 44, pp. 55-551) teach an absence of correlation between protein and mRNA levels for the Reg protein. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. Guo et al (Journal of Pharmacology and Experimental Therapeutics, 2002, vol. 300, pp. 206-212) teach that Oatp2 mRNA levels did not show a correlation with Oatp2 protein levels, suggesting that regulation of the Oatp2 protein occurs at both the transcriptional and post-translational level. These references serve to demonstrate that levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational. Clearly, to determine whether the polypeptide encoded by SEQ ID NO:1 is overexpressed in breast cancer as compared to normal controls requires additional experimentation and the claimed invention does not have substantial utility.

Further, the asserted utilities of the encoded polypeptide and fragments thereof drawn to DNA-binding, dimerization and transcriptional activities appear to be based on computer based comparison of SEQ ID NO:2 to databases in order to determine functional activity for sequences of SEQ ID NO:2. In particular the

specification teaches that Urb-ctf contains a bZIP domain conferring DNA-binding activity/transcriptional regulatory activity, it also has a leucine zipper providing dimerization activity (pages 3 and 4). The specification teaches assays for determinaton of these activities (p. 3), none of which appear to have been used to determine activity. Further, although the specification teaches that SEQ ID NO:2 has these domains, the specification does not teach that SEQ ID NO:2 has the consensus sequences required for those domains. It cannot be determined from the information in the specification whether the sequence has those consensus domains or whether the assignment of those domains to SEQ ID NO:2 is based on sequence similarity of unknown identity. Further, the specification does not teach the portion of DNA that SEQ ID NO:2 binds, does not teach what SEQ ID NO:2 dimerizes with, does not teach any specific transcriptional activity of the encoded polypeptide, that is what protein its transcriptional activity is directed to. If it were to be assumed that the cited domains function as suggested, the activity of these domains is not specific to SEQ ID NO:2 because they apply to many unrelated polypeptide structure sequences. Further, assuming for examination purposes that the functional domains of SEQ ID NO:2 were identified by sequence comparisons, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still

insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the error rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399 para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrongly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). In particular, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport protein family since the putative protein had a 29% identity to rat sulfate-anion transporter, 32% similarity to human

diastrophic dysplasia sulfate transporter and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport activity wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al suggest that these results underscore the importance of confirming the function of newly identified gene products even when database searched reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).. Thus, it cannot be predicted, nor would it be expected, based on the teachings of Bork and Scott that the identified domains would function as claimed. Thus, additional work must be done in order to determine if the encoded polypeptide does in fact function as suggested. Thus the claimed invention does not have a substantial utility.

Finally, the asserted utility of the claimed polynucleotide appears to be based on the identity of the encoded polypeptide with the polypeptide encoded by AK014463. It is noted that the specification teaches that SEQ ID NO:2 shares 97% identity with the polypeptide encoded by AK014463. However a search of the 67 databases of the STN Bioscience group did not reveal a single reference that teaches that a function was known for the AK014463 encoded polypeptide at the time the invention was made. Thus, the claimed invention does not have a well-established utility based on its homology to the polypeptide encoded by AK014463.

Since neither the claimed polynucleotide nor the encoded polypeptide have either substantial or well-established utility, none of variants of the polynucleotides encoding fragments of SEQ ID NO:2 have either substantial or well-established

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utility. Finally, neither the specification nor any art of record teaches what the claimed polynucleotide or encoded polypeptide variants and fragments thereof are, what they do, do not teach a relationship to any specific disease or establish any involvement of the claimed polynucleotide or encoded polypeptide in the etiology of any specific disease. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids. Because the claimed invention is not supported by a specific asserted utility, a substantial utility, a well established utility for the reasons set forth, credibility of any utility cannot be assessed.

Applicant is invited to submit objective evidence demonstrating, for example, that the claimed invention is in fact differentially expressed in breast cancer tissue as compared to a normal breast cancer tissue control in order to overcome the rejection under 35 USC 101.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."
9. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph.

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Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

10. In the event that Applicants might be able to overcome the 35 USC 101 and 35 USC 112, first paragraph rejection above, Claims 1-8 would still be rejected as the specification would still be enabling only for claims limited to polynucleotides comprising SEQ ID NO:1 and the complete complement thereof because the specification does not reasonably provide enablement for polynucleotides that encode SEQ ID NO:2, polynucleotides that encode a fragment of SEQ ID NO:2, polynucleotide sequences having 97% identity/99% identity to SEQ ID NO:1, polynucleotides which code for a polypeptide comprising at least eight amino acids, an isolated polynucleotide which is effective in a polymerase chain reaction.

It is noted that although claim 2 is drawn to "An isolated of claim 1" it will be assumed for examination purposes that claim 2 is drawn to an isolated polynucleotide of claim 1.

The claims are drawn to polynucleotides that encode SEQ ID NO:2, polynucleotides that encode a fragment of SEQ ID NO:2, polynucleotide sequences having 97% identity/99% identity to SEQ ID NO:1, polynucleotides which code for a polypeptide comprising at least eight amino acids, an isolated polynucleotide which is effective in a polymerase chain reaction.

As drawn to claims 1, 2, 5-8 and the recitation "complement thereof". One cannot extrapolate the teaching of the specification to the enablement of the claims because claims 1, 2, 5-8 encompass polynucleotides comprising non-disclosed

nucleic acid sequences attached to SEQ ID NO:1 and polynucleotides that encode SEQ ID NO:2, that is polynucleotides that are a complement of those molecules. The specification teaches that the term complementary refers to base pairing between nucleotides (p. 9, lines 1-5). The specification does not provide a limiting definition of the term “a complement”, thus it is assumed for examination purposes that a complement may be a partial complement or a complete complement. A review of the “Nucleic Acid Sequences” section of the specification doe not reveal any discussion of “complements”. However, it is conventional and well known in the art, as taught by US Patent No. 5,912,143, that the term complementary refers to the natural binding of polynucleotides under permissive salt and temperature conditions and specifically teaches that complementarity between two single-stranded molecules may be “partial” or it may be “complete” (col 5, lines 19-32). When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims **would not** share either structural or functional properties with SEQ ID NO:1 or polynucleotides that encode SEQ ID NO:2 or encode proteins that share either structural or functional properties with Urb-ctf. The specification fails to provide an enabling disclosure for how one would use such polynucleotides. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed

invention. The rejection may be obviated, for example, by amending the claims to recite “the complete complement”.

As drawn to claims 7 and 8. The claims as currently constituted read on polynucleotides which do not include a sequence that encodes more than a single nucleotide of SEQ ID NO:2. When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the complementary polynucleotides encompassed by the claims **would not** share either structural or functional properties with SEQ ID NO:1 or polynucleotides that encode SEQ ID NO:2 or encode proteins that share either structural or functional properties with Urb-ctf. The specification fails to provide an enabling disclosure for how one would use such polynucleotides. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art on how to use the broadly claimed species. For the above reasons, undue experimentation would be required to practice the claimed invention. The rejection of claim 8 may be obviated, for example, by amending the claim to recite “a polynucleotide effective in polymerase chain reaction wherein said polynucleotide consists of “ and then add a particular number of residues of SEQ ID NO:1 or by amending the claim to recite that the polymerase chain reaction amplifies SEQ ID NO:1..

As drawn to claims 3-6, the claims are drawn to variants of SEQ ID NO:1, polynucleotides encoding polypeptides comprising fragments of SEQ ID NO:2, that variants of SEQ ID NO:2. However, it is well known in that the art of protein

chemistry is highly unpredictable. For example, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al ( J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often

dramatically affect the biological activity and characteristics of a protein. Clearly, the claims are drawn to variants of the claimed polynucleotide that range from 1% variance to 99.9993% (that is wherein the encoded polypeptide comprises a single amino acid of SEQ ID NO:2 as claimed in claims 5 and 8) variance of the claimed polynucleotide. Given the teachings of Bowie et al, Burgess et al, Lazar et al, above, it cannot be predicted, nor would it be expected that the broadly claimed polynucleotides would encode polypeptides which would function in the same manner as SEQ ID NO:2. Given the above, it would require undue experimentation in order to use the claimed invention.

11. Claims 1, 2, 5-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to polynucleotides comprising a polynucleotide sequence encoding an amino acid sequence of SEQ ID NO:2, which reads on polynucleotides encoding two amino acids of SEQ ID NO:2 as claimed in claim 1, polynucleotides comprising polynucleotide sequence encoding one, two amino acids set forth in SEQ ID NO:2 as claimed in claim 5, polynucleotides comprising polynucleotide sequence encoding polypeptides comprising fragments of SEQ ID NO:2 as claimed in claim 6, unidentified complements of a polynucleotide encoding SEQ ID NO:2/SEQ ID NO:1, .

The specification discloses an isolated cDNA sequence, SEQ ID NO: 1, which encodes a predictive polypeptide sequence, SEQ ID NO. 2. Absent evidence to the contrary, each of the SEQ ID NOS elected for examination is deemed to be an incomplete cDNA. Because the cDNAs that correspond to the SEQ ID NOS mentioned in the claims are not full-length, a sequence prepared from undefined parts of a cDNA clone will not comprise the entire coding region of any particular gene, nor is it clear that the partial sequence is even in frame to encode a polypeptide (It is noted that the Applicant admits on the record that using GenomeScan, predictions revealed at least two different predicted genes instead of the single gene, Urb-ctf described in the specification, see p. 2, lines 28-30). The claims, as written, however, encompass polynucleotides which vary substantially in length and also in nucleotide composition. The broadly claimed genus additionally, encompasses genes, as well as genes incorporating only portions of the disclosed sequence.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive

structural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by using standard hybridization and PCR screens. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed and no identifying characteristic or property of the instant polynucleotides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

The specification further fails to identify and describe the 5' and 3' regulatory regions and untranslated regions essential to the function of the claimed invention, which are required since the claimed invention currently encompasses the gene. The art indicates that the structures of genes with naturally occurring regulatory elements and untranslated regions is empirically determined (Harris et al. J. of The Am Society of Nephrology 6:1125-33, 1995; Ahn et al. Nature Genetics 3(4):283-91, 1993; and Cawthon et al. Genomics 9(3):446-60, 1991). Therefore, the structure of these elements is not conventional in the art and skilled in the art would therefore not recognize from the disclosure that applicant was in possession of the genus of nucleic acid, including genes, comprising SEQ ID NO: 1 or fragments thereof.

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Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

***Claim Rejections - 35 USC § 102***

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

12. Claims 1, 5, 6,12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93).

The claims are drawn to an isolated polynucleotide comprising a polynucleotide sequence which codes an amino acid sequence set forth in SEQ ID NO:2 or a complement thereof (claim 1), an isolated polynucleotide comprising a polynucleotide sequence selected from SEQ ID NO:1 wherein a single or double amino acid is claimed, or a complement thereof (claim 5), an isolated polynucleotide comprising a polynucleotide coding for segments of SEQ ID NO:2 or a complement thereof.

The Boehringer Mannheim teaches random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924) a subset of which will be a complement of the claimed polynucleotides. All of the limitations of the claims are met.

13. Claims 1, 5, 8 are rejected under 35 USC 102(b) as being anticipated by Carninci et al (Genome Research, 2000, 10(10) 1617-1630) or Shibata et al (Genome Research, 2000) 10(11) 1757-1771.

It is noted that the specification teaches that the present invention relates to an isolated polynucleotide which is specific for human Urb-ctf and which codes for a polypeptide comprising for example the amino acids disclosed in Claim 5 (p. 6, lines 20-28). Thus it is assumed for examination purposes, since Claim 5 claims a polynucleotide encoding amino acid 38 of SEQ ID NO:2 which is proline, amino acid 68 which is alanine, amino acid 119 which is alanine, amino acid 161 which is serine, amino acid 583 which is threonine, amino acid 606 which is glutamine, amino acids 76-77 which are glycine-lysine, that any polynucleotide that codes for

any of these specific amino acids in any position of the polypeptide is specific for human Urb-ctf.

The claims are drawn to are drawn to an isolated polynucleotide comprising a polynucleotide sequence which encodes an amino acid sequence set forth in SEQ ID NO:2, an isolated polynucleotide comprising a sequence which is specific for Urb-ctf and which codes for a polypeptide, said polypeptide comprising one of amino acids 68, 38, 119, 161, 583, 606, 76-77 of SEQ ID NO:2, wherein the polynucleotide codes for a polypeptide comprising at least eight amino acids in length.

Carninci et al and Shibata et al teach an isolated nucleic acid molecule which encodes a polypeptide comprising amino acids that are identical to one of amino acids 68, 38, 119, 161, 583, 606, 76-77 of SEQ ID NO:2, 68, 76-77 of SEQ ID NO:2 (see sequence database search us-10-054-935-2.rst, result 1) wherein the encoded polypeptide comprises more than eight amino acids. All of the limitations of the claims are met.

14. Claims 5 and 7 is are rejected under 35 USC 102(b) as being anticipated by Konno et al (AL049450), Genbank Sequence Database (Acession AL049450), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available June 23, 2000.

It is noted that the specification teaches that the present invention relates to an isolated polynucleotide which is specific for human Urb-ctf and which codes for a polypeptide comprising for example the amino acids disclosed in Claim 5 (p. 6, lines 20-28). Thus it is assumed for examination purposes, since Claim 5 claims a

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polynucleotide encoding amino acid 38 of SEQ ID NO:2 which is proline, amino acid 68 which is alanine, amino acid 119 which is alanine, amino acid 161 which is serine, amino acid 583 which is threonine, amino acid 606 which is glutamine, amino acids 76-77 which are glycine-lysine, that any polynucleotide that codes for any of these specific amino acids in any position of the polypeptide is specific for human Urb-ctf.

The claims are drawn to are drawn to an isolated polynucleotide comprising a polynucleotide sequence which encodes an amino acid sequence set forth in SEQ ID NO:2, an isolated polynucleotide comprising a sequence which is specific for Urb-ctf and which codes for a polypeptide, said polypeptide comprising one of amino acids 68, 38, 119, 161, 583, 606, 76-77 of SEQ ID NO:2, wherein the polynucleotide is effective in a polymerase chain reaction.

Konno et al teach AL049450, a partial cDNA which Applicant admits on the record codes for 198 amino acids of SEQ ID NO:2. Although the reference does not specifically teach that the partial cDNA will be effective in a polymerase chain reaction, the claimed polynucleotide appears to be the same as the prior art polynucleotide, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable

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differences. See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray* 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

15. No claims allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

  
Susan Ungar  
Primary Patent Examiner  
July 21, 2003